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Dynamic vapor sorption for quality assessment of pharmaceutical coatings: a case study in enteric protection

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This study investigates the performance of different enteric coating systems by integrating dynamic vapor sorption (DVS), optical coherence tomography (OCT), and acid-stage dissolution testing to evaluate moisture sensitivity, structural integrity, and acid resistance of coated pharmaceutical tablets. Omeprazole-containing tablets were coated with three commercially available enteric systems and analyzed using DVS to assess sorption kinetics under controlled humidity and temperature conditions. OCT was employed to non-destructively evaluate coating thickness and uniformity. Functional performance was determined *via* acid-stage dissolution testing following FDA guidelines for delayed-release formulations. The DVS results revealed marked differences in moisture uptake behavior among the coatings, while OCT imaging identified variability in coating distribution, both of which were found to correlate with dissolution outcomes. Coatings with lower hygroscopicity and more consistent thickness profiles demonstrated acid resistance. These findings underscore the value of combining DVS and OCT as complementary analytical tools for the comprehensive evaluation of enteric coatings, enabling improved formulation design and quality control aligned with Quality by Design (QbD) principles.

1. Introduction

Pharmaceutical tablet coatings serve multiple critical purposes in the design and functionality of oral solid dosage forms. Beyond their traditional roles in improving tablet appearance, masking unpleasant tastes, and facilitating swallowing, coatings are essential in modulating drug release profiles and protecting active pharmaceutical ingredients (APIs) from environmental or physiological degradation.[1,2] Enteric coatings represent advanced functional coating systems engineered to withstand gastric acidity and facilitate drug release in the more neutral to basic environment of the intestine. This is especially important for acid-labile APIs, such as omeprazole, where premature degradation in gastric fluid can drastically reduce bioavailability and therapeutic efficacy.[1,3] In addition to protecting acid-labile APIs, enteric coatings are widely used for drugs that can induce gastric mucosal irritation.[4] By enabling delayed release in the intestinal environment, these systems help mitigate local irritation, as observed for non-steroidal anti-inflammatory drugs such as diclofenac.[4]

A major challenge in developing robust enteric-coated tablets lies in controlling moisture uptake during manufacturing, storage, and transportation. Many enteric polymers, such as methacrylate-based or cellulose-derived systems, exhibit varying degrees of hygroscopicity, which can compromise film integrity and functional performance over time.[5] Excess moisture can plasticize or weaken the polymer matrix, leading to cracking, swelling, or porosity, all of which may result in premature drug release in acidic conditions. Therefore, evaluating the moisture sorption behavior of coating systems is critical for predicting stability and ensuring consistent product quality.[1,5]

In this context, Dynamic Vapor Sorption (DVS) offers a highly sensitive and reproducible method for assessing how coating materials interact with humidity under controlled conditions. DVS measures changes in sample mass as a function of relative humidity (RH) and time, providing detailed sorption/desorption isotherms and kinetic data.[6] This allows for precise characterization of the rate and extent of moisture uptake, hysteresis effects, and potential transitions in material state (*e.g.*, glass transition, recrystallization). Compared to conventional gravimetric or loss-on-drying methods, DVS enables dynamic monitoring of moisture exchange at microgram sensitivity, making it especially suitable for studying small quantities of excipients and coatings.[6,7]

However, while DVS provides valuable information about the moisture behavior of coatings, it does not directly reveal

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information about their structural attributes, such as thickness, homogeneity, or uniformity, which are equally important determinants of functionality. To address this, Optical Coherence Tomography (OCT) has emerged as a powerful non-destructive imaging technique for the real-time evaluation of coated pharmaceutical products.[8] OCT enables high-resolution, cross-sectional imaging of coatings in three dimensions, allowing for the visualization of layer structure, detection of defects, and quantitative measurement of coating thickness across tablet surfaces. Unlike traditional destructive methods such as cross-section microscopy, OCT preserves the integrity of the sample, supports in-process monitoring, and offers the potential for integration into process analytical technology (PAT) frameworks.[9–11]

The combination of DVS and OCT provides a complementary analytical approach to assessing enteric coatings. Together, these methods can offer predictive insights into a coating's ability to provide effective acid resistance. To validate these physicochemical and structural findings, acid-stage dissolution testing is employed as a functional readout. According to USP ⟨711⟩ and FDA guidelines, enteric-coated tablets must withstand a defined duration in acidic media (typically 0.1 N HCl for two hours) without releasing a significant amount of the API.[3,12,13] Variations in dissolution profiles can then be linked back to observed differences in coating integrity (*via* OCT) and moisture sorption behavior (*via* DVS).

In this study, we evaluated three different enteric coating systems by integrating DVS, OCT, and acid-stage dissolution testing. Each system is assessed for its moisture sorption capacity, coating uniformity, and acid resistance, enabling a multidimensional characterization of coating performance. By combining the complementary insights obtained from each technique, this work aims to establish a more comprehensive and predictive framework for coating quality evaluation.

This study aims to establish a robust analytical methodology for evaluating enteric coatings by combining OCT and DVS under the framework of Quality by Design (QbD).[14,15] This dual approach enhances method understanding and performance prediction by addressing structural (coating thickness and uniformity *via* OCT) and functional (moisture sorption behavior *via* DVS) attributes. This integrated methodology offers a predictive, science-based platform for formulation optimization and quality assurance throughout the product lifecycle.[14,16,17]

2. Materials and methods

2.1. Materials

2.1.1. Reagents and chemicals. Acetonitrile (Reag. Ph. Eur., suitable for HPLC gradient elution), used both as a mobile phase component and diluent, was procured from M&B Stricker Laborfachhandel GbR (Bernried am Starnberger See, Germany). Buffer solution for the mobile phase was prepared using ammonium bicarbonate (BioUltra, ≥99.5% purity) and 25% ammonia solution, both from Sigma-Aldrich (St Louis, United States). Additional reagents included sodium hydroxide (Dri™, ≥97% purity), and hydrochloric acid (37%) from Sigma-Aldrich. All analytical and sample preparation procedures utilized purified water generated by Triton UV purification system (Neptec, Elbtal, Germany). Sample filtration was performed using nylon syringe filters (0.22 μm) supplied by YETI Merz Brothers GmbH (Haid, Austria).

2.1.2. Standards, samples, and excipients. Omeprazole powder (100% purity) was procured from Shenzhen Nexconn Pharmatechs Ltd (Shenzhen, China). MicroceLac®, a co-processed excipient consisting of 75% alpha-lactose monohydrate and 25% microcrystalline cellulose, was obtained from MEGGLE GmbH & Co. (Wasserburg, Germany). Sodium starch glycolate (EXPLOTAB®, Type A) and sodium stearyl fumarate (PRUV®) were supplied by JRS Pharma (Polanco, Spain). Subcoating of the tablet cores was carried out using Opadry® II, a clear polyvinyl alcohol-based film coating system from Colorcon (Harleysville, USA). The enteric top-coating systems used in this study included Aquarius™ control ENA from Ashland (Wilmington, USA), along with Acryl-EZE®, Nutrateric®, Surelease® (25% solids ethylcellulose dispersion), and NS Enteric®, all sourced from Colorcon (Harleysville, USA).

The formulation prototype and manufacturing process were previously established based on earlier studies.[18,19] The tablet formulation is shown in Table 1, and the manufacturing process is described in SI (Tables S1 and S2). For this study, only tablets that were compliant with acid-stage dissolution requirements,[20] as demonstrated in previous experiments,[19] were included.

2.2. Methods

2.2.1. Omeprazole content determination and dissolution *via* UPLC. The determination of omeprazole was made by high-performance liquid chromatography (HPLC), carried out using an Acquity UPLC H-Class® system (Waters, Milford, United States) equipped with a photodiode array (PDA) detector and an XBridge BEH C18 XP 130 Å column. System control and data acquisition were managed *via* Empower 3 chromatographic software (Waters, Milford, United States). pH measurements were performed using a FiveEasy pH meter (Mettler Toledo, Columbus, United States). The analytical method was validated previously in accordance with ICH Q2(R2) guidelines,[21] and the specific chromatographic conditions are provided in the SI (Tables S3 and S4).

Acid-stage dissolution testing was conducted on an Agilent 708-DS dissolution apparatus (USP Apparatus II, Agilent Technologies, Santa Clara, United States), following FDA rec-

Table 1 Formulation of core omeprazole tablets

Component	mg	%
Omeprazole	20	10
MicroceLac®	170	85
EXPLOTAB®	8	4
PRUV®	2	1
Total	200	100

ommendations for over-the-counter omeprazole delayed-release tablets.[13] Six coated tablets (n = 6) were placed in 750 mL of 0.1 N hydrochloric acid and stirred at 100 rpm for two hours. Following acid exposure, the media were neutralized, and drug extraction was performed using a buffer/acetonitrile mixture. Samples were filtered through 0.22 µm nylon syringe filters prior to HPLC analysis.

2.2.2. Coating evaluation *via* optical coherence tomography (OCT). The OCT acquisition method used in this study was previously established in-house.[10,19] Measurements were performed on six tablets prior to acid-stage dissolution testing. Tablets were placed on a rotating disc (Schuett-biotec, Göttingen, Germany), and images of both convex surfaces and the band were captured using an industrial OCT system with a 1D-OCT probe (OSeeT Pharma 1D HW 2.0, Phyllon GmbH, Graz, Austria). Each scan lasted one minute to ensure consistency. The system operated at 100 000 A-scans per second, with axial and lateral resolutions of 4.1 µm and 14 µm, respectively. Image acquisition and analysis were carried out using OSeeT 3.4.12 software.

OCT images were analyzed for coating thickness, and homogeneity within and across tablets. A refractive index of 1.5 was applied for all coatings, based on previously values (Table S4),[22] as minor differences were not expected to impact the quality focus of this analysis on DVS. Coating distribution data were processed using Microsoft Excel 2013 (Microsoft, Redmond, United States).

2.2.3. Coating evaluation *via* dynamic vapor sorption (DVS). Moisture sorption behavior of the coated tablets and uncoated tablet core was assessed using a DVS system (DVS-Resolution, 1, Surface Measurement Systems Ltd, London, UK). The instrument features an SMS UltraBalance with dynamic range of ±150 mg and ±0.1 µg resolution enclosed in a temperature-controlled chamber (±0.1 °C). One tablet with approximately 230 mg initial weight was placed in the sample pan, and an counterweight with 100 mg was placed in the reference pan. The tablet was dried in at 25 °C under dry nitrogen flow until the change of weight was less than 0.002% min^{-1} over 10 min to obtain the reference (dry) mass of the tablet. The tablet was then exposed to a controlled humidity ramp from 0–90% RH over 180 minutes. Gravimetric data points were collected at 10-second intervals to determine sorption kinetics.

Water uptake was expressed as percentage mass change from the reference (dry) mass of the tablet.

3. Results and discussion

3.1. Coating thickness and dissolution determination in the acid stage

Coating thickness for both the sub-coating and enteric layers was measured using OCT, following the non-destructive methodology established in literature.[19] These measurements confirmed that all coated tablets had thickness values within the compliant range previously validated for acid resistance.[19,23] In addition to average thickness, OCT data were evaluated for intra-tablet thickness variability as an indicator of coating uniformity (Fig. 1). All three enteric coatings showed low relative standard deviations of thickness across top, band, and bottom regions, consistent with visually homogeneous layers (Table 2).

Subsequently, the same tablets were individually subjected to acid-stage dissolution testing to verify functional performance. As expected, given the consistent coating architecture confirmed by OCT, all samples remained within pharmacopeial limits,[12] demonstrating appropriate resistance to acidic conditions. The combined use of OCT and dissolution testing,

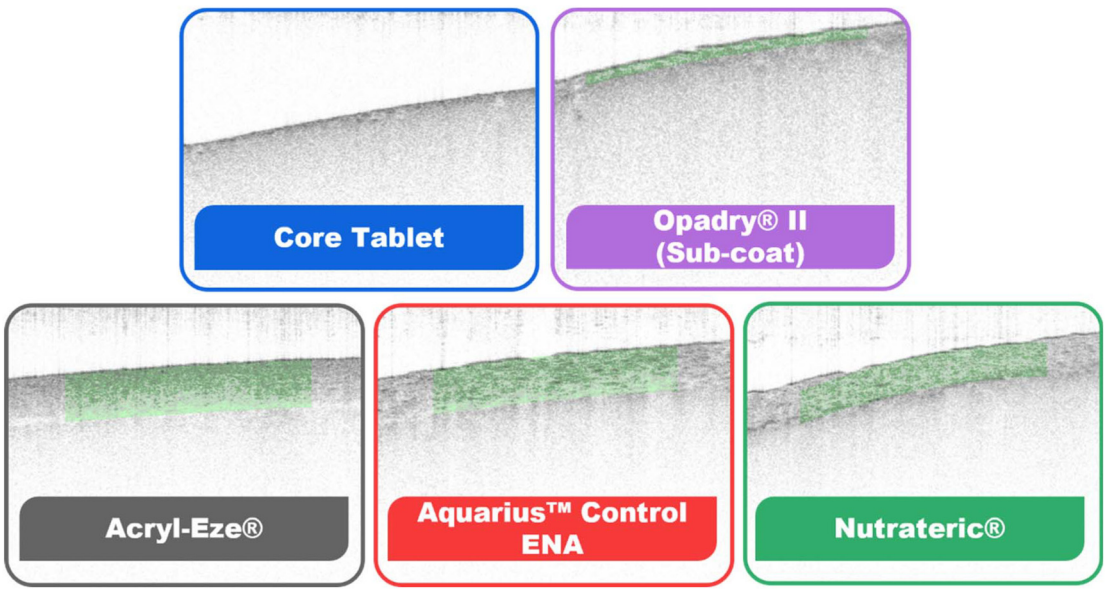

Fig. 1 OCT cross-sectional images of selected enteric-coated tablet formulations, showing the surface at the top. The automated coating layer detection is highlighted in green, displaying the detected layers.

Table 2 Results for coating thickness *via* OCT on enteric-coated tablet formulations in all tablet positions

Formulation	Average thickness (μm)			Thickness specification[a] (μm)
	Top	Band	Bottom	
Opadry® II	18.7 ± 2.7	16.7 ± 2.7	18.6 ± 2.5	N.A.
Acryl-Eze®	137.1 ± 5.3	91.0 ± 5.1	140.0 ± 8.4	NLT 68
Aquarius™ control ENA	125.4 ± 4.8	85.8 ± 7.2	125.0 ± 6.2	NLT 69
Nutrateric®	101.2 ± 6.2	79.9 ± 1.9	101.3 ± 3.1	NLT 65

[a] Specifications based on A1 acid stage compliance (USP ⟨711⟩).

as illustrated in Fig. 2. This reinforces the value of OCT as a predictive tool for verifying structural quality prior to *in vitro* evaluation.

To further investigate the relationship between coating structure and functional performance, individual tablet data were plotted to correlate coating thickness with acid-stage dissolution (Fig. 2). For each formulation, simple exponential trendlines were fitted as visual aids, and the corresponding regression equations and coefficients are provided in the SI (Table S5). This approach, previously supported in the literature,[19] enabled a comparative assessment of acid resistance performance across coatings. These trendlines are not intended as predictive models, but only as a first qualitative approximation illustrating that all formulations comply with the pharmacopeial acid-stage limit and substantial variability in drug release persists even at comparable thickness levels.

While the mean coating thicknesses differed to some extent between formulations, they all fell within a relatively narrow range (approximately 100–140 μm; Table 2) and were above the previously established minimum thickness required for acid protection. Nevertheless, the dissolution results still showed clear differences in protective performance. Acryl-EZE® displayed the most consistent acid resistance, with low and relatively uniform release values. Control ENA also maintained adequate protection, though with slightly greater variability. In contrast, Nutrateric® exhibited the highest and most variable release, despite comparable coating thickness. The data scatter indicates that additional factors, such as polymer composition, film microstructure (*e.g.*, porosity and local inhomogeneities), process conditions, and the intrinsic variability of dissolution testing, also contribute significantly to the observed behavior and should be considered alongside thickness.

These findings indicate that coating thickness alone is not sufficient to fully explain acid resistance. Instead, intrinsic material properties and microstructural features, such as porosity or inhomogeneities, likely play a significant role. While OCT provides valuable information on coating thickness and macroscopic uniformity, it is inherently limited in detecting sub-visible defects that may compromise barrier integrity.[24] This limitation underscores the need for complementary analytical techniques, such as DVS, to assess coating permeability. By quantifying moisture uptake under controlled conditions, DVS helped reveal formulation-specific differences in barrier performance, providing a more complete understanding of how enteric coatings behave under both storage and physiological stress conditions.

3.2. Coating permeation method development *via* DVS

The DVS method was developed in alignment with key principles of Analytical Quality by Design (AQbD), including risk-based parameter selection and method optimization, to ensure that the analytical procedure was scientifically justified and fit for its intended purpose. The key objective was to develop a methodology capable of differentiating the moisture permeability of various tablet prototypes, including the

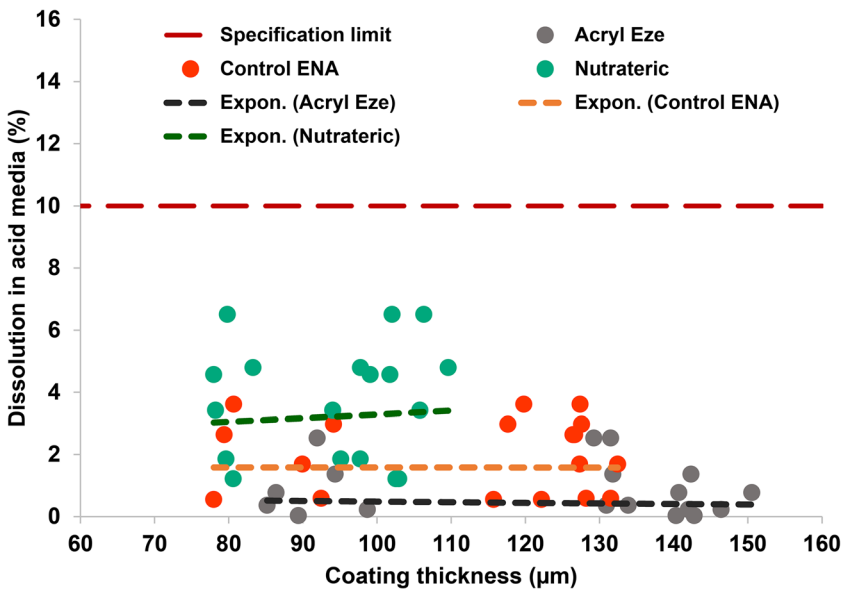

Fig. 2 OCT-measured coating thickness *vs.* acid-stage dissolution for omeprazole enteric-coated prototypes.

uncoated core, sub-coated tablets (Opadry® II only), and enteric-coated formulations.

3.2.1. Analytical target profile (ATP), risk assessment and identification of critical method parameters (CMPs). The ATP was defined as the ability of the DVS method to detect and quantify differences in water vapor sorption behavior among coated prototypes under controlled temperature and relative humidity (RH) conditions. The method must demonstrate sufficient discriminatory power to detect differences in sorption kinetics and equilibrium moisture content (EMC) that are relevant to the prediction of coating barrier performance and product stability. Our proposed ATP performance criteria are described in Table 3.

A clear ATP guides the selection of method parameters, and ensures that the final method supports both scientific and eventual regulatory objectives, such as material selection, formulation optimization, and quality risk management.[14,25,26]

Afterwards, a risk-based approach was used to identify the CMPs that could impact method performance. A semi-quantitative risk assessment matrix evaluating the CMPs for the DVS methodology under a regular AQbD framework (Table 4). Each CMP was scored based on its impact (on method performance) and uncertainty (degree of knowledge or control), with a higher risk priority score indicating a greater need for method control or further study.

The impact reflects the expected influence of each parameter on the ability of the method to meet the ATP, while the uncertainty reflects the level of prior knowledge and control. For example, balance sensitivity was assigned the highest impact,[5] because insufficient mass resolution would directly compromise detection of subtle differences in moisture uptake (<1%), and high uncertainty[4] because this is instrument-specific and must be empirically verified. In contrast, data acquisition frequency was assigned lower impact and uncertainty (2/2), since preliminary experiments showed that 10-s acquisition intervals were more than sufficient to capture the sorption kinetics without information loss. The risk priority score (impact × uncertainty) was then used to prioritize parameters for control and further optimization.[27]

3.2.2. Experimental design and refinement towards discrimination power. Initial experimental trials were conducted to evaluate the hygroscopicity of the uncoated tablet core to variations in relative humidity. The pronounced hygroscopicity of the core was considered a prerequisite for enabling the detection of differences in water uptake arising from varying levels of coating protection. In this context, a highly moisture-responsive core facilitates the discrimination of coating performance, as differences in permeability can be amplified at the system level.

A preliminary dynamic vapor sorption (DVS) experiment was performed using a multi-step isotherm protocol, consisting of 18 steps from 0% to 90% RH and back to 0% RH. Each step was maintained for 60 minutes or until the mass change was ≤0.01%.[28] Under these conditions, the tablet core exhibited a mass increase of approximately 2% (≈4 mg) within ~200 minutes (Fig. 3), confirming its high sensitivity to humidity and suitability for subsequent coating evaluation.

Given the high sensitivity of the system and the analytical resolution of the instrument, the feasibility of continuous ramp methods was subsequently explored as an alternative to conventional multi-step isotherms. Traditional stepwise methods are known to introduce history effects, whereby prior humidity exposure influences subsequent sorption behavior due to structural or physicochemical changes within the material, while also significantly extending analysis time.[29] To address these limitations, a modified test protocol was designed, consisting of an initial drying step (until mass change ≤0.002%), followed by two continuous humidification ramps (0–90% RH within 60 minutes), each followed by immediate drying phases.

As shown in Fig. 4, the ramp-based approach effectively differentiated between coated and uncoated tablets, as well as among the different coating systems. These differences were reflected not only in the total mass uptake but also in the sorption–desorption kinetics, evidenced by distinct curve shapes and hysteresis patterns. Such behavior is indicative of differences in coating permeability and moisture transport mechanisms, including diffusion and polymer relaxation phenomena.[29]

Based on these findings, a robust analytical protocol was established comprising a controlled drying phase (mass change ≤0.002% over 10 minutes or a maximum duration of 6 hours), followed by a single-step relative humidity ramp from 0% to 90% over 180 minutes. This optimized method enabled efficient discrimination of coating systems while significantly reducing analysis time compared to traditional DVS isotherms.

All measurements were conducted at 25 °C, with data acquisition at 10-second intervals and a mass resolution of ±0.1 μg. Equilibrium during the drying phase was defined as a mass change ≤0.002% over a 10-minute interval, or a maximum

Table 3 ATP performance criteria for DVS method development

Parameter	Target/requirement
Sensitivity	Ability to detect mass changes ≤0.1 μg
Reproducibility	%RSD ≤5% for sorption/desorption profiles across triplicates
Discrimination power	Statistically significant differentiation ($p < 0.05$) between coating types

Table 4 Semi-quantitative risk assessment matrix for the evaluation of CMPs for the DVS methodology

CMP	Impact (1–5)	Uncertainty (1–5)	Risk priority score
Sensitivity	5	4	20
Relative humidity step size	2	2	12
Stop criteria definition	3	3	12
Sample mass	3	2	9
RH equilibration time	4	2	12
RH control accuracy	4	3	12
Sample conditioning (pre-drying)	4	3	9
Temperature control	3	2	6
Data acquisition frequency	2	2	4

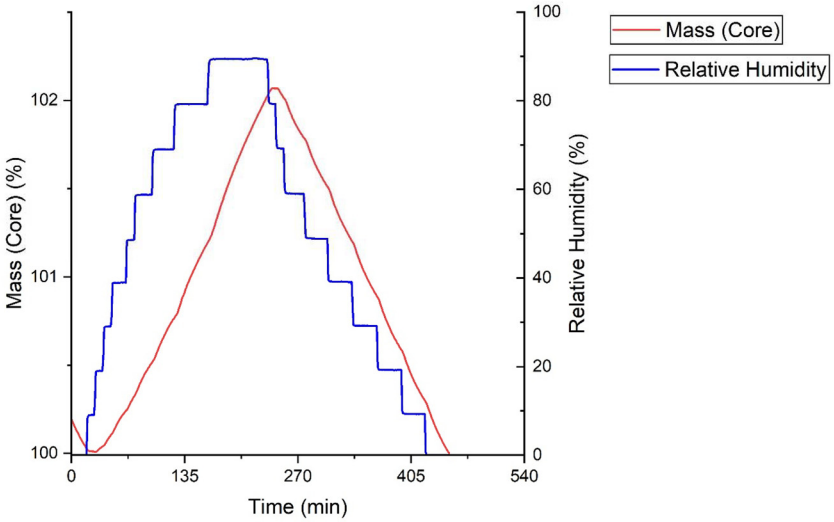

Fig. 3 Preliminary DVS sorption profile of the tablet core.

drying time of 6 hours if this criterion was not achieved. These conditions ensured method robustness and reproducibility while maintaining a practical analytical timeframe, in line with AQbD principles for method development.

Is noticeable that during method development we compared traditional multi-step isotherms with continuous RH ramps. The stepwise protocol met the sensitivity criterion but required extended run times and showed pronounced history effects. In contrast, continuous ramps delivered comparable sensitivity with improved discrimination between prototypes within a shorter experimental time. The final protocol (single ramp 0–90% RH over 180 min following a controlled drying step) was selected because it fulfilled all ATP criteria (Table 3). Resulted into maximized discrimination between coatings (Fig. 5–7), while maintaining high repeatability and a practical runtime.

All measurements were conducted at 25 °C, and data were collected at 10-second intervals with a mass resolution of ±0.1 μg. Equilibrium during the drying phase was defined as a mass change ≤0.002% over a 10-minute interval, or a maximum drying time of 6 hours if this criterion was not met. These conditions ensured method consistency while maintaining a practical analysis time.

3.3. Coating permeation findings *via* DVS

The developed DVS method was applied to assess and compare the moisture permeability of five tablet prototypes: the uncoated core, the sub-coated formulation with Opadry® II, and three enteric-coated systems (Acryl-EZE®, Aquarius™ control ENA, and Nutrateric®). The resulting sorption profiles, shown in Fig. 5 and 6, demonstrate clear and consistent differentiation in water vapor uptake across the formulations, confirming the method's strong discriminatory capability.

As expected, the core tablets exhibited the highest moisture sorption, with a steep exponential increase in delta mass as RH rises, particularly beyond 20% RH. This reflects the core's complete lack of moisture barrier protection and serves as a positive control for high permeability. The Opadry® II sub-coated tablets showed a clear reduction in water uptake compared to the core, validating the sub-coating's partial barrier function. However, the sorption curve still increased significantly above 75% RH, indicating that the Opadry® II layer alone is insufficient for long-term protection in humid conditions.

Among the enteric coatings, Nutrateric® showed higher moisture uptake than both Acryl-EZE® and Aquarius™ control ENA, particularly at RH levels above 50%. This may reflect differences in polymer composition and film morphology, such as porosity or hydrophilicity.[19,30,31] In contrast, Acryl-EZE® and Aquarius™ control ENA demonstrated the most favorable moisture barrier properties, with relatively flat and overlapping sorption profiles and minimal change in delta mass even at elevated RH.[32,33] This suggests their potential superiority in terms of stability under humid storage conditions.

While the present work primarily focused on macroscopic layer thickness and overall moisture uptake, the observed differences between coating systems are also consistent with differences in film microstructure. Coating porosity and density are strongly influenced by spray rate, solids content of the coating dispersion, inlet/outlet temperature, and drying kinetics during film formation.[34,35] Higher drying rates and sub-optimal coalescence can lead to more porous, defect-rich films, which in turn increase effective permeability even at comparable overall weight gain.

In our study, the DVS profiles of Nutrateric® compared to Acryl-EZE® and Aquarius™ control ENA suggest a more permeable and possibly more open microstructure, consistent with the higher moisture uptake despite similar OCT-measured thickness ranges. Although we did not directly quantify porosity or density, these microstructural attributes provide a plausible mechanistic explanation for the formulation-dependent differences in permeability and acid resis-

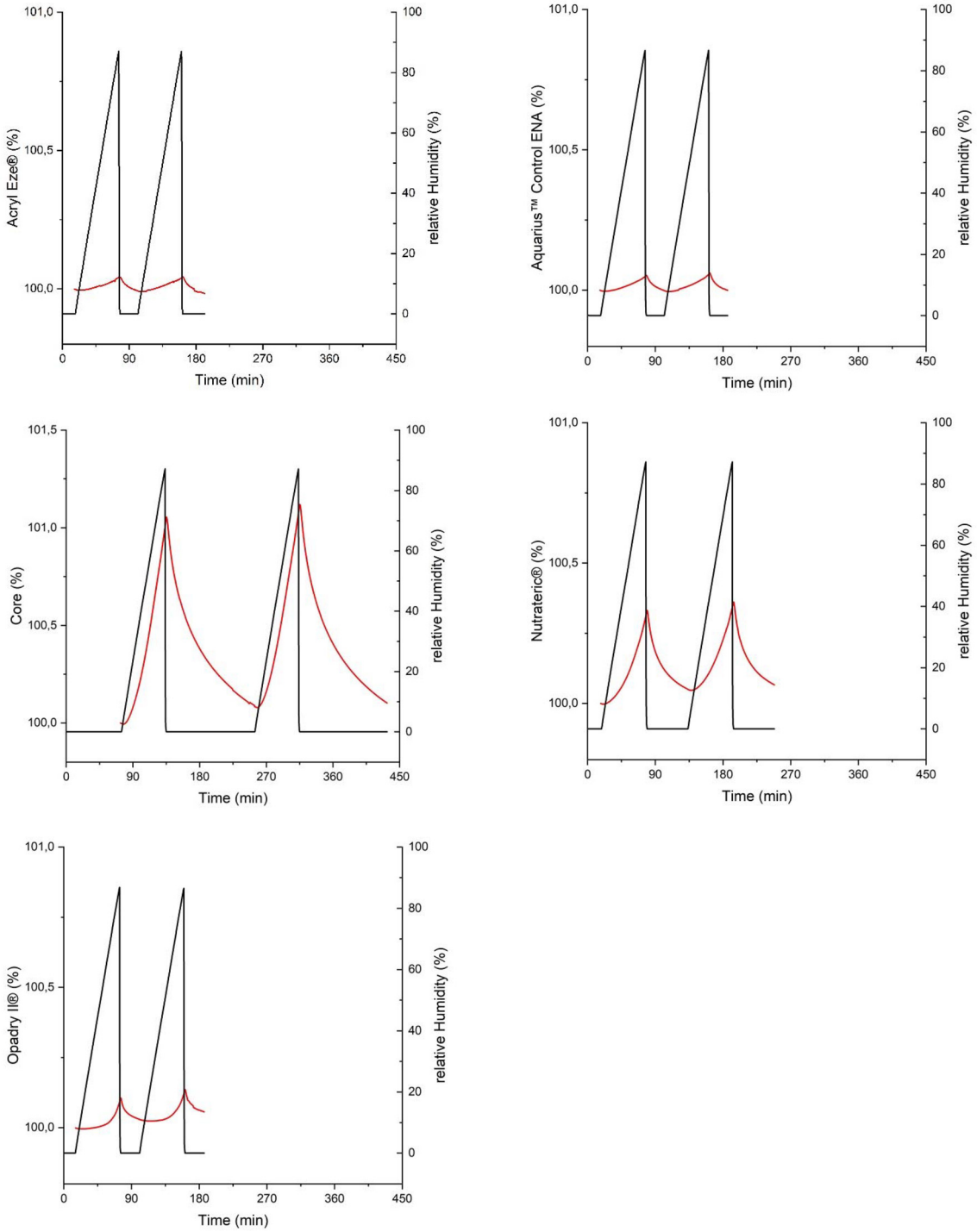

Fig. 4 Feasibility ramp tests of different coating materials. Red curves represent mass change (%) relative to the dry tablet (100%). All coated tablets reached the drying criterion (≤0.002% mass change) in significantly shorter times.

tance observed. Future work should incorporate direct porosity measurements (*e.g.*, mercury porosimetry or X-ray micro-CT) to deconvolute thickness from microstructure effects.[36]

The zoomed-in graph (Fig. 6) further emphasizes these differences at lower RH values, where subtle but consistent gaps between formulations become visible. The fact that these distinctions were observable with relatively small changes in moisture uptake (sub-1%) speaks to the sensitivity and robustness of the method, which was carefully designed under the AQbD framework to enable this level of resolution. Importantly, based on the standard deviations all profiles indicate excellent repeatability and low method variability.

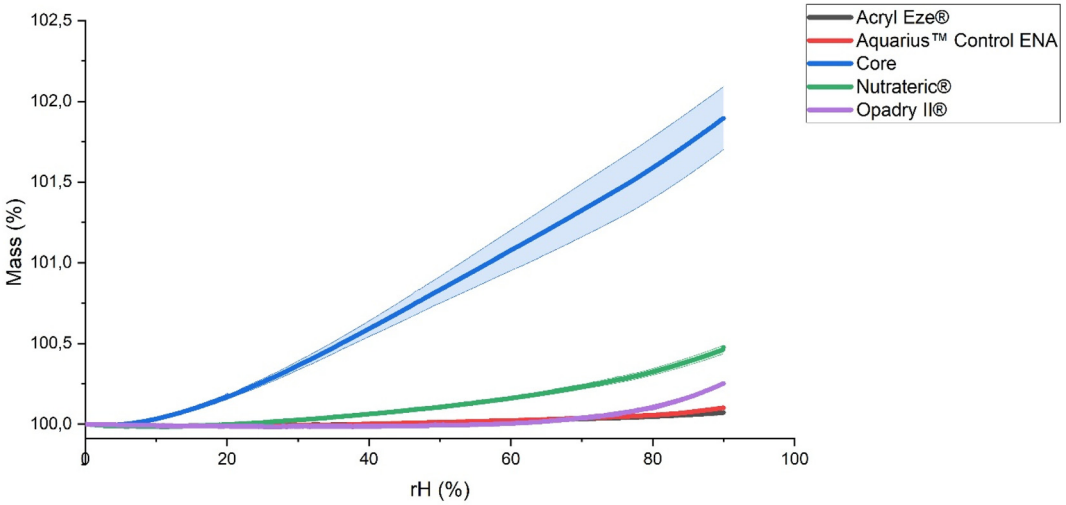

Fig. 5 DVS mass change profiles of coated tablets and core showing coating-dependent moisture uptake behavior.

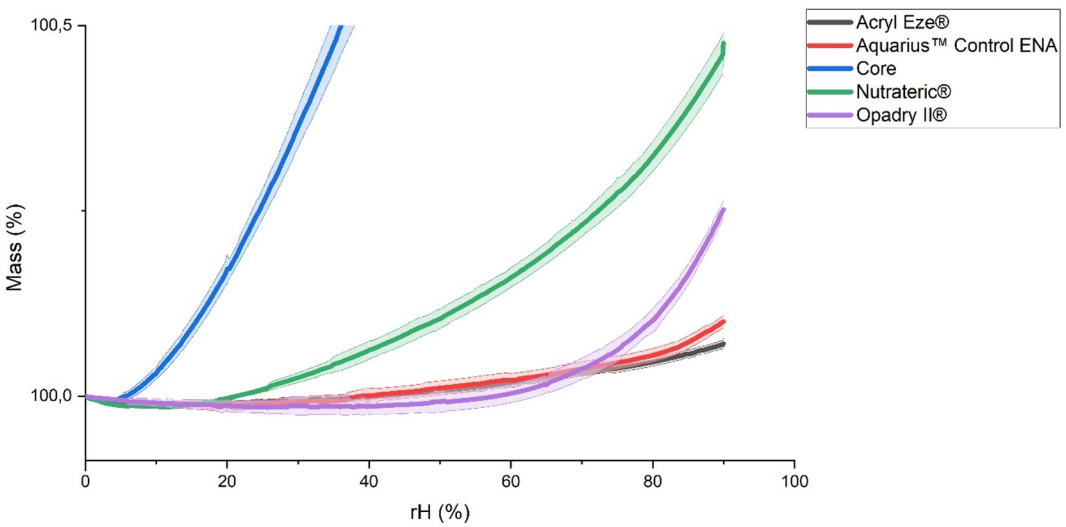

Fig. 6 Zoomed DVS mass change profiles emphasizing differences in coating permeability.

To evaluate the sensitivity of the DVS method to coating damage, mechanical defects were deliberately introduced into a subset of tablets using a predefined scratching procedure applied in a standardized manner immediately before analysis. This experiment served as a qualitative proof of concept to verify that DVS can discriminate between intact and deliberately compromised coatings and was not intended to establish a quantitative relationship between defect size and moisture uptake. Consistent with this objective, the resulting DVS profiles clearly demonstrate the capability of the method to distinguish between intact and mechanically damaged coatings, with the extent of differentiation being strongly dependent on the intrinsic permeability of each coating system (Fig. 7).

As expected, the uncoated core shows no meaningful difference between intact and damaged conditions, confirming that the introduced mechanical defect does not alter the inherent hygroscopic behavior of the tablet matrix itself. This observation supports that the detected differences for coated systems are exclusively attributable to coating performance rather than core variability.

For Opadry II®, the intact coating demonstrates moderate moisture uptake, while the damaged samples show a clear increase in sorption, particularly at higher RH. This suggests that while Opadry II® provides a certain degree of moisture protection, its barrier properties are more sensitive to structural disruption (Fig. 7).

For Acryl Eze®, the intact and damaged profiles remain relatively close across the entire RH range, with only a slight increase in mass uptake for the damaged samples at higher humidity levels (Fig. 7). This behavior indicates a comparatively low permeability system, where even after mechanical disruption, the overall moisture ingress remains limited.

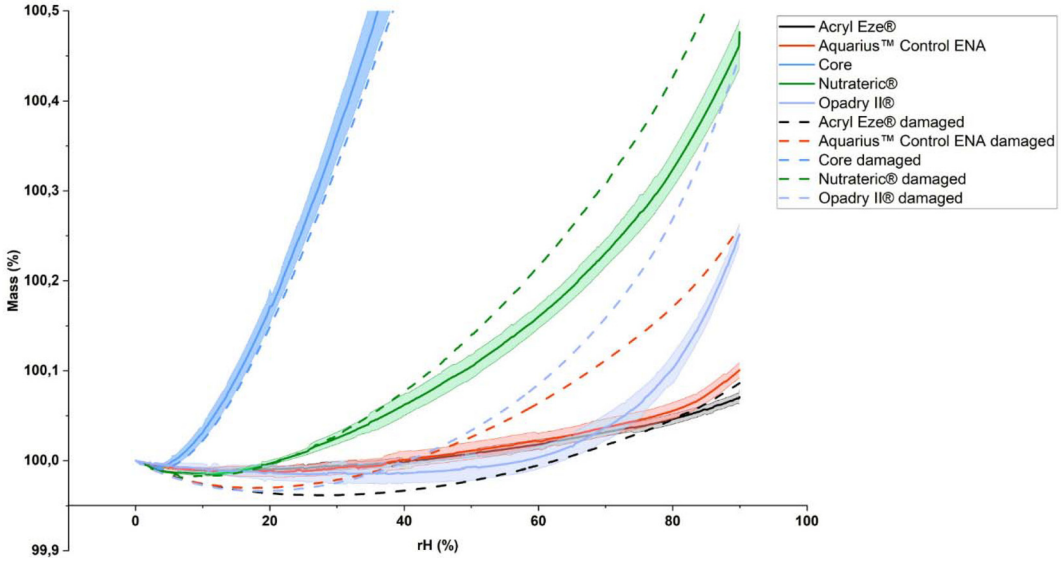

Fig. 7 DVS moisture sorption behavior of intact *versus* mechanically damaged coated tablets highlighting differences in coating permeability.

Interestingly, the damaged samples initially exhibit a slightly lower mass (desorption trend at low RH), which may be attributed to the release of previously trapped moisture within the tablet during the damaging process. This suggests that Acryl Eze® provides an effective barrier not only against external moisture ingress but also contributes to retaining internal moisture, highlighting its protective character.

A similar trend is observed for Aquarius™ control ENA, although the separation between intact and damaged samples is more pronounced at elevated RH (Fig. 7). The intact coating maintains low moisture uptake, consistent with a relatively dense and homogeneous structure. Upon damage, the increase in sorption becomes more evident, indicating that the barrier function is compromised but still partially maintained. As with Acryl Eze®, a minor desorption effect at lower RH suggests that the coating system may initially retain moisture, reinforcing its role as a protective barrier.

In contrast, Nutrateric® exhibits a markedly different behavior. Even in the intact state, the coating shows higher moisture uptake compared to the other systems, indicating a more permeable one. Upon mechanical damage, this difference becomes significantly amplified, with the damaged profile diverging strongly from the intact curve, particularly at intermediate to high RH levels (Fig. 7). This pronounced sensitivity suggests that Nutrateric® relies more heavily on coating integrity to maintain its barrier function, and once compromised, moisture penetration is rapidly facilitated. The results highlight a lower tolerance of this to structural defects, making it more susceptible to performance variability.

3.4. Combined assessment of coating quality

Overall, the DVS results confirm that the method possesses strong discriminatory power to detect coating damage (Fig. 7), even when such defects are not directly observable by structural techniques such as OCT.[37,38] The magnitude of separation between intact and damaged profiles provides valuable insight into the robustness and permeability of each coating system. In this context, DVS effectively characterizes the functional permeability of different coatings and enables differentiation between formulations that may appear equivalent based on physical attributes alone, such as coating thickness or uniformity.[19] This functional sensitivity is particularly relevant for identifying sub-visible defects and understanding their impact on performance. These findings are complemented by the acid-stage dissolution results (Fig. 2), which confirm that all coating systems meet the pharmacopoeial acceptance criteria limits,[12] demonstrating adequate enteric protection at a global level. However, dissolution testing alone does not provide sufficient sensitivity to discriminate between coating systems, as all formulations comply with the specification despite exhibiting different permeability profiles. In this context, DVS provides additional discriminatory power by revealing differences in moisture transport behavior that are not captured by dissolution testing, thereby offering a more sensitive and predictive assessment of coating performance.

The relationship between coating permeability and acid resistance is a fundamental aspect governing the performance of enteric-coated dosage forms.[39] Enteric coatings are designed to act as a barrier against gastric fluid, preventing drug release in acidic conditions while allowing dissolution at higher intestinal pH.[40] This protective function is directly linked to the permeability of the coating film, as acid penetration occurs through the same mechanisms governing moisture transport as adsorption at the surface, diffusion through the polymer matrix, and desorption at the core interface.[41,42] The relationship between water vapor diffusion and the polymer film can be described by Crank's equation:[41]

$$P = D \times S$$

where P is the permeability coefficient, D the diffusion coefficient, and S the solubility of the penetrant within the polymer matrix.[39] This relationship highlights that permeability is governed by both the mobility of the penetrant through the film and its affinity for the polymer.

In this study, Crank's equation is used in a conceptual manner to relate moisture diffusion and solubility within the polymer matrix to the observed sorption profiles. Due to the complex geometry of intact coated tablets and the absence of independent measurements of film area and effective diffusion path length, we did not attempt to extract absolute permeability coefficients from the DVS data. Instead, we interpret differences in moisture uptake and sorption kinetics as relative indicators of effective permeability among the coating systems. Consequently, coatings with lower permeability to water and hydrogen ions provide enhanced acid resistance, as they effectively delay or prevent the ingress of gastric media into the tablet core.[40,43,44] Coatings with higher permeability results from increased hydrophilicity, lower polymer density, or the presence of microstructural defects; that eventually facilitate faster transport of moisture and acidic media, leading to premature drug release.[43,45–47] In contrast, dense and homogeneous coatings with low permeability act as efficient diffusion barriers, maintaining protection during the acid stage. This explains why, in enteric-coated prototypes like, Acryl Eze® and Aquarius™ control ENA prototype exhibiting lower moisture uptake in DVS experiments typically demonstrate favorable acid resistance, while more permeable systems show increased variability and higher release under acidic conditions, as on the Nutrateric® prototype. Importantly, these differences are not fully explained by coating thickness alone, reinforcing that permeability-related attributes govern functional performance. Moisture uptake measured by DVS is a composite outcome influenced by intrinsic polymer properties (hygroscopicity, glass transition), coating thickness, porosity, and overall coating integrity. In the present study, thickness and macroscopic uniformity were controlled and quantified *via* OCT, but we did not independently quantify porosity or microcrack density. Therefore, the DVS data are interpreted as a functional measure of 'effective permeability' of the complete coating system, rather than as a direct readout of any single structural parameter. In this context, the modest differences in average coating thickness observed between formulations (Table 2) are unlikely to fully account for the pronounced separation of the DVS sorption profiles. All coatings exhibit thicknesses above the OCT-derived specification limit for gastro-resistance, and substantial differences in moisture uptake and sorption kinetics persist even where thickness values overlap. We therefore interpret the discriminatory response of the DVS method as being primarily driven by formulation-dependent differences in coating permeability and integrity, while acknowledging that a minor contribution from thickness effects cannot be completely excluded. This integrated interpretation is consistent with previous work linking DVS-derived sorption kinetics to combined effects of diffusion and polymer relaxation.[41,42] It also highlights a limitation of the present study: although DVS is highly sensitive to subtle differences in barrier performance, it cannot by itself deconvolute the relative contributions of thickness *vs*. microstructure, which motivates future studies combining DVS with direct microstructural characterization.

Overall, these findings highlight permeability as a critical functional quality attribute linking coating physicochemical properties to *in vitro* performance. Taken together, defining an ATP, performing risk-based CMP assessment, and refining the DVS protocol to maximize discrimination between coating systems exemplify the application of AQbD principles to analytical method development. This reinforces the value of DVS as a complementary analytical tool that captures critical quality attributes linked to moisture transport, supporting its application within an QbD framework. Such insight is essential for rational formulation development, appropriate material selection, and reliable stability prediction, especially for sensitive APIs such as omeprazole.

4. Conclusions

This study demonstrated a comprehensive analytical strategy for the evaluation of enteric-coated tablet systems by integrating DVS, OCT, and acid-stage dissolution testing under the framework of QbD. OCT provided non-destructive, high-resolution structural data on coating thickness and uniformity, while dissolution testing verified functional acid resistance. However, to overcome OCT's limitations in detecting subsurface or microstructural defects, a robust DVS method was developed to assess moisture permeability as a critical quality attribute linked to coating integrity.

The DVS method, systematically developed through AQbD principles, successfully differentiated the water vapor sorption behavior across multiple prototypes, including the uncoated core, Opadry® II sub-coated tablets, and three enteric-coated formulations. Despite compliant coating thicknesses, the formulations exhibited clear differences in moisture uptake, highlighting the added value of functional permeability profiling. Among the tested systems, Acryl-EZE® and Aquarius™ control ENA displayed the most effective moisture barriers, correlating well with their acid protection performance.

Altogether, this integrated approach provides a predictive, multidimensional platform for evaluating enteric coatings; combining structural, functional, and environmental stress data. It supports more informed formulation decisions, enhances control strategies, and aligns with modern regulatory expectations for risk-based, science-driven product development.

Author contributions

Conceptualization, J. A. A. U.; methodology, M. P., J. A. A. U.; validation, A. S. N.; formal analysis, M. P., A. S. N., A. F. and J. A. A. U.; resources, J. A. A. U.; data curation, M. P.; writing –

original draft preparation, J. A. A. U.; writing – review and editing, M. P., A. S. N., A. F. and R. A. L. G.; visualization, J. A. A. U. and M. P.; supervision, J. A. A. U. and R. A. L. G.; project administration, J. A. A. U. and R. A. L. G.; funding acquisition, J. A. A. U. and R. A. L. G. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

All data and materials are present in the manuscript and supplementary information (SI). Supplementary information is available. See DOI: https://doi.org/10.1039/d6pm00129g.

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